Lineage-Specific Differentiation of Pluripotent Human Embryonic Stem Cells and its Implications for the Future of Cell Therapy

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IOM Committee on CIRM Review
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San Diego Regenerative Medicine Institute
Human Stem Cells — Key to Regeneration

Founded in 2010

Non-Profit Independent Research Institute for Human Embryonic Stem Cell (hESC) Research & Stem Cell Therapy Development

Leading Technology in human neuronal and cardiovascular regeneration from pluripotent hESCs to provide the next generation of cell based therapeutic solutions for unmet medical needs

Website: http://www.sdrmi.org

The Current State of The Art for Generating Functional Cells from Pluripotent Stem Cells Through Multi-Lineage Differentiation of Embryoid Bodies

uncontrollable, inefficient, instable, highly variable, difficult to reproduce and scale-up.

Conventional Multi-Lineage Differentiation of Pluripotent Cells

- Germ-Layer Induction
- Pluripotent Human Embryonic Stem Cells

- Selection & Enrichment
- Endoderm, Mesoderm, Ectoderm Cells

- Multipotent Stem/Progenitor/Precurser Cells

- Specialized Mature Cells
San Diego Regenerative Medicine Institute

Ground-Breaking Technology Platform

Lineage-Specific Differentiation of Pluripotent Human Embryonic Stem Cells

By Small Molecule Induction [PluriXcel-SMI]
San Diego Regenerative Medicine Institute
Clinical-Grade Human Cell Therapy Products

Direct Conversion of Pluripotent Human Embryonic Stem Cells into a Large Supply of Human Neuronal Cells for Cell Therapy

hESC-derived Human Cell Therapy Products for Neurological Diseases & Injuries

Human pluripotent/embryonic stem cell-derived Human neuronal progenitors & neurons [Xcel-hNuP001 & Xcel-hNu001]
San Diego Regenerative Medicine Institute
Clinical-Grade Human Cell Therapy Products

Direct Conversion of Pluripotent Human Embryonic Stem Cells into a Large Supply of Human Cardiomyocytes for Cell Therapy

hESC-derived Human Cell Therapy Products for Heart Disease

Human pluripotent/embryonic stem cell-derived human cardiac precursors & cardiomyocytes
[Xcel-hcardP001 & Xcel-hCM001]
California Stem Cell Research & Cure Bond Act (Proposition 71)

The New, Normal, Unlimited Potential, and Most Forefront Human Embryonic Stem Cell Research & Therapy Development
California Institute for Regenerative Medicine (CIRM)

The New, Normal, Unlimited Potential, and Most Forefront Human Embryonic Stem Cell Research & Therapy Development

No Scientific Merit of Prop71

The Old (gene, protein, antibody therapy)
Abnormal (cancer cells, cancer stem cells, iPS cells, reprogrammed adult cells)
limited Potential (adult stem cells, tissue-derived stem cells)
Outdated (mesenchymal cells, genetical-engineered cells)
Projects
California Stem Cell Research & Cure Bond Act (Proposition 71)

Score grant and loan award applications for **scientific merit**:

A demonstrated record of achievement in the areas of **pluripotent stem cell and progenitor cell biology and medicine**
“Developing human-pluripotent-stem-cell-derived neuron regeneration therapy for spinal cord repair”

**Scientific Merit of Prop71**

Novel efficient approach, New & better hESC-derived cell therapy product.

High stem/progenitor activity for nerve regeneration dramatically increase the clinical efficacy & safety targeting both acute and chronic patients much broader population than Geron’s trial.

Therapy development critical to Prop71

Unmet medical need & urgent to SCI patients

CIRM Has Never Brought Up for Consideration

Neither on Scored nor Not Scored List
CIRM DISEASE TEAM THERAPY DEVELOPMENT AWARDS (~$400M of Prop71)

No Scientific Merit of Prop71

The Old --- gene, protein, antibody therapies
Abnormal --- cancer cells, cancer stem cells, iPS cells, reprogrammed adult cells
limited Potential --- adult stem cells, tissue-derived stem cells
Outdated --- mesenchymal cells [5/6 went to UC Davis in the same round], endogenous cells, genetically-engineered cells

Despite those lack of stem/progenitor activity, high toxicity, immuno-rejection (not graftable), have failed multiple clinical trials previously
SDRMI Grant Application for
CIRM Early Translational II Research Awards Pre-Application RFA-11-02
TR3-05505 “Heart precursors directed from human embryonic stem cells for myocardium regeneration”

Scientific Merit of Prop71

Novel efficient approach, New & better hESC-derived cell therapy product
High stem/progenitor activity for heart muscle regeneration
dramatically increase the clinical efficacy & safety
Therapy development critical to Prop71
Unmet medical need & urgent to heart patients

Blocked by CIRM Non-Transparent Pre-Application
biased, conflict-of-interest, anti-Prop71-scientific-merit reviewer comments:
Target product indication is very vague (600 character limitation in the pre-app to allow data, description, and anything more than general statement)
The applicant does not address the issue of immunogenicity (hESCs and their derivatives considerably less immunogenic. None of CIRM awarded adult cell grants [e.g., 5/6 adult mesenchymal stem cells in one round] has addressed their major issue of immunogenicity)
No apparent experience in drug development (PI has demonstrated record in pluripotent stem/progenitor cells and cell therapy development of Prop71)
SDRMI Grant Application for
CIRM Basic Biology Awards IV **Pre-Application** RFA-11-03
RB4-06272 “MicroRNAs in Directing Pluripotent hESC Cardiac Lineage Specification To Cardiomyocytes”

**Scientific Merit of Prop71**

Innovative approach, cardiac lineage-specific differentiation of hESCs, Focus on genome-scale profiling of miRNAs in the cascade of hESC cardiac progression towards beating cardiomyocytes, essential for revealing molecular determinants in hESC cardiac fate decision and understanding of molecular cardiogenesis in human embryonic development.

**Blocked by CIRM Non-Transparent Pre-Application**

biased, conflict-of-interest, anti-Prop71-scientific merit reviewer comments:

Score : 2, Preliminary data is descriptive and qualitative; totally unclear how the differentiation protocol employed will enable analysis of "stages" of cardiomyogenesis; objectives lack focus, thus results expected to be too diffuse to provide any novel mechanistic insights.

(Abstract style, limits words and space, not allow data, description, and anything more than general statement, not enough information for score and critique)

Proposal eligible for CA stem cell research & bond act and critical to CIRM’s mission should be the first and only consideration for pre-selection of grants
Suggestions & Comments

CIRM/CIRM RFAs use California Stem Cell Research & Cure Bond Act to Fund human embryonic stem cell research & novel therapy development of Prop71 urgent to incurable diseases/patients

CIRM/CIRM RFAs use California Stem Cell Research & Cure Bond Act to support human embryonic stem cell research leaders and stem cell research leadership activity of Prop71

CIRM/CIRM RFAs have transparent grant review and funding process, such as eliminate the biased and non-transparent pre-application, allow applicant formal appeal for pre-application, give grant applicants the opportunity to speak/talk about their proposals in open public meetings

Urge California State Officials to nominate human embryonic stem cell research advocates and human embryonic stem cell therapy start-ups representatives to the ICOC board to represent the interest of California Stem Cell Research & Cure Bond Act (Prop71)
Suggestions & Comments

President Obama Signed Jobs Act to Jumpstart American Start-ups

CIRM use California Stem Cell Research & Cure Bond Act

Jumpstart human embryonic stem cell therapy Start-ups of Prop71

Xcelthera http://www.xcelthera.com

Stem Cell Therapy — Unleashing the Power of Life Sciences
Scientific Merit of Prop71

In Motion

Human embryonic stem cell-derived beating cardiomyocytes
lineage-specific differentiation of hESCs by small molecule induction
SDRMI Grant Application for
RFA 10-05 CIRM DISEASE TEAM THERAPY DEVELOPMENT AWARDS
Application Number DR2-05339
“Developing human-pluripotent-stem-cell-derived neuron regeneration therapy for spinal cord repair”

Scientific Merit of Prop71
In Motion

Mouse Transplanted with Human embryonic stem cell-derived neurons
By small molecule induction

Circular Movement (CIRM)